PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07C 29/03, C07D 401/14, 453/04

A1

(11) International Publication Number: WO 98/35927

(43) International Publication Date: 20 August 1998 (20.08.98)

(21) International Application Number: PCT/US97/02442

(22) International Filing Date: 14 February 1997 (14.02.97)

(71) Applicant *(for all designated States except US)*: THE SCRIPPS RESEARCH INSTITUTE [US/US]; 10550 North Torrey Pines Road, La Jolla, CA 92037 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: JANDA, Kim, D. [US/US]; 3181 Erie Street, San Diego, CA 92117 (US). HAN, Hyunsoo [KR/US]; 4120–85 Porte De Merano, San Diego, CA 92122 (US).

(74) Agents: LEWIS, Donald, G. et al.; The Scripps Research Institute, 10550 North Torrey Pines Road, TPC–8, La Jolla, CA 92037 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: PEG–BOUND ALKALOID LIGANDS AND USE THEREOF

(57) Abstract

Polyethylene glycol monomethyl ether–bound alkaloid ligands (PEG–bound alkaloid ligands) are constructed and employed in the ligand–accelerated catalytic (LAC) Sharpless asymmetric dihydroxylation reaction (AD) with a range of olefins. The PEG serves as a scaffold which allows simple product separation, polymer–bound ligand recovery, and recycling of the chiral liquid phase support without a loss of catalytic activity or ligand acceleration.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

PEG-BOUND ALKALOID LIGANDS AND USE THEREOF

Description

Technical Field of the Invention:

The present invention relates to ligand-accelerated catalytic (LAC) Sharpless asymmetric dihydroxylation reactions (AD) of olefins. More particularly, the present invention relates to polyethylene glycol (PEG) bound alkaloid ligands employable in the ligand-accelerated catalytic (LAC) Sharpless asymmetric dihydroxylation reaction (AD) of olefins and to their synthesis and use.

Background of the Invention:

A variety of methods have been developed for recycling rare and/or valuable reagents and catalysts. In a conventional methodology, the reagent or catalyst is coupled to an insoluble support prior to its use in a reaction. After the reaction is complete, the reagent or catalyst is isolated and then recycled by isolating the insoluble support. The recycled reagent or catalyst attached to its insoluble support may then be re-employed in further reactions. Examples of this methodology have been developed for a number of reagents and catalysts. (Pittman et al. Comprehensive Organometallic Chemistry; Wilkinson, G., Ed.; Pergamon Press: Oxford, 1982; Mathur et al. Polymers as Aids in Organic Chemistry. Academic Press: New York, 1980; Frechet et al. Tetrahedron 1981, 37, 663; Sherrington et al. Syntheses and separations Using Functionalized Polymers; Wiley: New York, 1988; Bergbreiter et al. J. Polym. Sci., Polym. Chem. Ed. 1989, 27, 4205).

Although such insoluble reagents and catalysts are

successfully employed in many applications, there are recognized limitations associated with their use. (Barany et al. In The Peptides, Vol. 2; Gross, E.; Meienhofer, J., Eds.; Academic Press: New York, 1979, p. 1). The insolubility of the reagents and catalysts can be disadvantageous before, during, and after the reaction. Particular disadvantages include the following:

(1) Formation of the reagent or catalyst on the support can be more tedious.

(2) Reagent or catalyst characterization is less than routine.

(3) Insolubility can limit the range of substrates and/or the polymer-bound reagent/catalysts utility.

(4) Insolubility can cause the reagent/catalyst reactivity to behave somewhat differently than its soluble (solution) counterpart.

(5) Non-linear kinetics have frequently been observed with insoluble supports.

Because of the above disadvantages, alternative strategies have been developed for recycling valuable reagents and catalysts. In one successful strategy, the reagents or catalysts are supported by soluble homopolymers. (Bayer et al. Angew.Chem. Int. Ed. 1975, 14, 493; Bayer et al. CHEMTECH 1976, 6, 212; Bergbreiter et al. ACS Symposium Series 1986, 308, 17; Bergbreiter et al. J. Am. Chem. Soc. 1987, 109, 174; Bergbreiter et al. CHEMTECH 1987, 17, 686; Phelps et al. Tetrahedron Lett. 1989, 30, 3915; Bergbreiter et al. J. Org. Chem. 1989, 54, 2726; Bergbreiter et al. Tetrahedron Lett. 1991, 32, 2731; Doyle et al. J. Org.

Chem. 1992, 57, 6103; Bergbreiter et al. J. Am. Chem. Soc. 1993, 115, 9295). In this strategy, the reactions are carried out homogeneously, i.e., without an insoluble phase, and the separation of the homopolymer from reaction products is achieved by taking advantage of the properties of the polymer chain. In the arena of combinatorial synthesis, this strategy is termed "Liquid Phase Combinatorial Synthesis" or LPCS. (Han et al. Proc. Natl. Acad. Sci. USA 1995, 92, 6419.) The key element of LPCS is a linear homopolymer, e.g., polyethylene glycol monomethyl ether (MeO-PEG), which serves a dual role as both a terminal protecting group and a solubilizing agent for any compound(s) synthesized on the support. Combinatorial peptide, small molecule, and peptidomimetic libraries can be synthesized using this approach.(Han et al. J. Am. Chem. Soc. 1996, 118, 2539.)

The ligand-accelerated catalytic (LAC) asymmetric dihydroxylation (AD) of olefins based on cinchona alkaloid ligands was described by Sharpless in 1988. (Jacobsen et al. J. Am. Chem. Soc. 1988, 110, 1968.) Since this seminal report, the AD reaction has been further developed to include application to a wider range of olefins, improved enantiomeric efficiency, and overall simplicity of operation (Kolb et al. Chem. Rev. 1994, 116, 2483). From the standpoint of cost, ligand and/or metal recovery and recycling are of prime interest because the cinchona alkaloid ligand and osmium tetroxide are the most expensive components of the procedure. Olefins have also been asymmetrically dihydoxylated using insoluble polymer bound cinchona alkaloid-ligands. (Kim et al. Tetrahedron Lett.. 1990, 31, 3003; Pini et al. Tetrahedron Lett. 1991, 32, 5175; Lohray et al. Tetrahedron Lett. 1992, 33, 5453; Pini et al. Tetrahedron: Asymmetry 1993, 4, 2351; Lohray et al. Tetrahedron Lett. 1994, 35, 6559; Pini et al.

Tetrahedron 1994, 50, 11321; Pini et al. Tetrahedron Lett. 1995, 36, 1549; Sung et al. Tetrahedron: Asymmetry 1995, 6, 2687). While this methodology represents a major improvement with respect to convenience and economics, it is deemed less than satisfactory because of increased reaction times, highly variable yields and lower enantioselectivity than had previously been obtained with its solution phase counterpart. A report by Salvadori and co-workers describes an insoluble support that provides improved enantioselectivity. However, their system still required long reaction times (24 hours) and excess of polymeric ligand. Furthermore, reaction yields were lower than observed under homogeneous reaction conditions. (Petri et al., Chirality 1995, 7, 580.)

The problems associated with LAC in which the ligand is localized by attachment to an insoluble polymer can be understood by considering the basic tenet upon which this concept is based (Berrisford et al. Angew. Chem. Int. Ed. Engl. 1995, 34, 1059). During LAC, the addition of a ligand increases the reaction rate of an already existing catalytic transformation. Both the ligand-accelerated and the nonaccelerated reactions operate in solution simultaneously and in competition with each other. If the ligand does not have equivalent access to all the reaction compartments where the substrate, metal oxidant and olefin reside, the most fundamental requirement for a successful ligand accelerated catalysis scenario is not met. For the present case, this means that the chiral ligand resides only in the insoluble phase while the OsO_4 and olefin are in solution and free to react anywhere. In this situation the optimal LAC conditions can probably never be achieved even when using a large excess of the insoluble polymer-bound ligand. (Petri et al. Chirality 1995, 7, 580.)

Since its discovery in 1988, Sharpless' catalytic asymmetric dihydroxylation (AD) of olefins has been continuously refined by both a development of better ligands and improvements in the secondary oxidant/solvent system. (For review, see: Kolb et al. *Chem. Rev.* **1994**, *116*, 2483; Becker et al. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 448). In parallel, Sharpless (Kim et al. *Tetrahedron Lett.* **1990**, *31*, 3003) and other groups (Pini et al. *Tetrahedron Lett.* **1991**, *32*, 5175; Lohray et al. *Tetrahedron Lett.* **1992**, *33*, 5453.; Pini et al. *Tetrahedron: Asymmetry* **1993**, *4*, 2351; Lohray et al. *Tetrahedron Lett.* **1994**, *35*, 6559; Pini et al. *Tetrahedron* **1994**, *50*, 11321; Pini et al. *Tetrahedron Lett.* **1995**, *36*, 1549; Sung et al. *Tetrahedron: Asymmetry* **1995**, *6*, 2687; Petri et al. *Chirality* **1995**, *7*, 580; Song et al. *Tetrahedron: Asymmetry* **1996**, *7*, 645) have investigated immobilization of these expensive ligands onto insoluble polymer supports so as to aid in their recovery. While this strategy provides a simple but elegant way for automating the AD reaction, it has a number of limitations including prolonged reaction times and, more importantly, a reduction in enantioselectivity

What is needed is a soluble polymer-bound ligand which provides all the advantages that an insoluble support can offer including ease of product separation and polymer-bound ligand recover/ reusability while also being as effective as a free ligand both in reactivity and selectivity. Furthermore, the new soluble polymer bound-ligand system should be applicable to other classes of AD ligands for improved enantioselectivity as well as other enantioselective catalytic processes.

Brief Summary of the Invention:

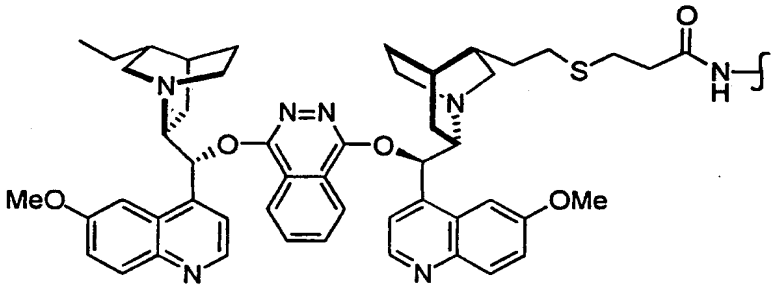
The invention relates to polyethylene glycol monomethyl ether-bound alkaloid ligands (termed liquid phase ligands) which are constructed and employed in the

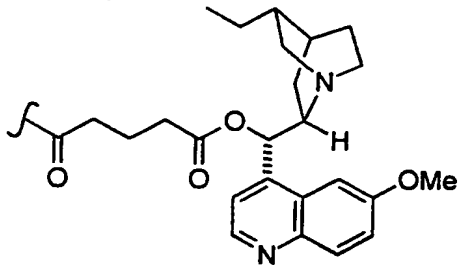
ligand-accelerated catalytic (LAC) Sharpless asymmetric dihydroxylation reaction (AD) with a range of olefins. These soluble polymer-bound ligands are much more efficient than the corresponding insoluble polymer-bound ligands both in reactivity and selectivity in AD reactions. In addition, these chiral homopolymers provide the same enantioselectivity and reactivity as free ligands in solution. Furthermore, the polymer serves as a scaffold allowing simple product separation, polymer-bound ligand recovery, and recycling of the chiral liquid phase support without a loss of catalytic activity.

One aspect of the invention is directed to a PEG bound alkaloid ligand. This PEG bound alkaloid ligand includes a polyethylene glycol which is soluble in aqueous medium and precipitable in aqueous/ether medium, and an alkaloid ligand coupled to the polyethylene glycol. Preferred alkaloid ligands are selected from the following group, viz.:

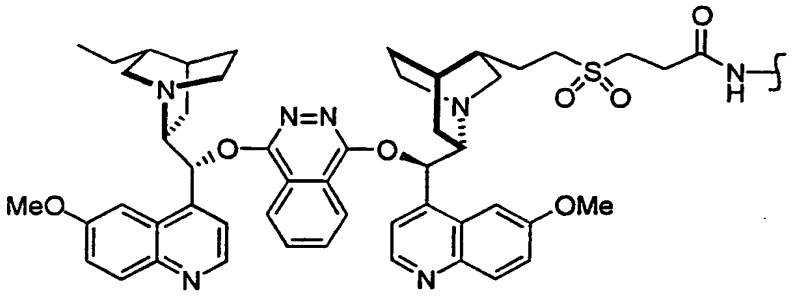
1,4-bis-(9'-O-dihydroquinidyl)-phthalazine;
1,4-bis-(9'-O-quinidyl)-phthalazine;
3,6-bis-(9'-O-dihydroquinidyl)-pyridazine;
3,6-bis-(9'-O-quinidyl)-pyridazine; 1,4-bis-
(9'-O-dihydroquinyl)-phthalazine;
1,4-bis-(9'-O-quinyl)-phthalazine;
3,6-bis-(9'-O-dihydroquinyl)-pyridazine;
3,6-bis-(9'-O-quinyl)-pyridazine;
dimethylcarbamoyl dihydroquinidine;
benzoyl dihydroquinidine;
4-methoxybenzoyl dihydroquinidine;
4-chlorobenzoyl dihydroquinidine;
2-chlorobenzoyl dihydroquinidine;
4-nitrobenzoyl dihydroquinidine;
3-chlorobenzoyl dihydroquinidine;
2-methoxybenzoyl dihydroquinidine;
3-methoxybenzoyl dihydroquinidine;

2-naphthoyl-dihydroquinidine;
cyclohexanoyl dihydroquinidine;
p-phenylbenzoyl dihydroquinidine;
dimethylcarbamoyl dihydroquinidine;
benzoyl dihydroquinine;
4-methoxybenzoyl dihydroquinine;
4-chlorobenzoyl dihydroquinine;
2-chlorobenzoyl dihydroquinine;
4-nitrobenzoyl dihydroquinine;
3-chlorobenzoyl dihydroquinine;
2-methoxybenzoyl dihydroquinine;
3-methoxybenzoyl dihydroquinine;
2-naphthoyl dihydroquinine;
cyclohexanoyl dihydroquinine;
p-phenylbenzoyl dihydroiquinone;
acrylonitrile co-polymer of 9-(4-chlorobenoyloxy)-quinidine;
acrylonitrile co-polymer of 11-((2-acryloyloxy)ethyl-sulfinyl)-9-(4-chlorobenoyloxy)-10,11-dihydroquinidine;
acrylonitrile co-polymer of 11-[2-acryloyloxy)ethylsulfonyl]-9-(N,N-dimethylcarbamoyl)-10,11-dihydroquinidine;
acrylonitrile co-polymer of 9-(10-undecanoyl)-10,11-dihydroquinidine; and
alkaloid ligands represented by the following structures:

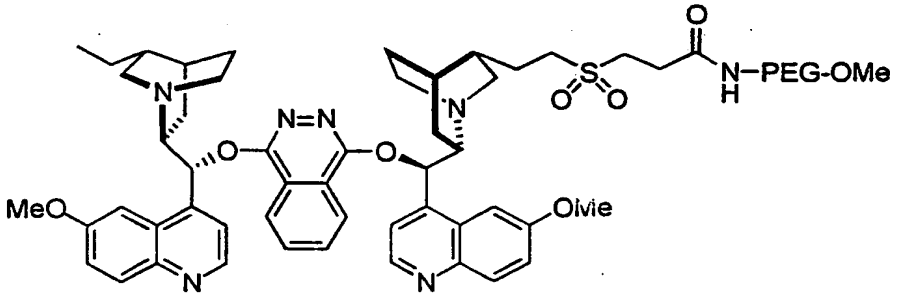


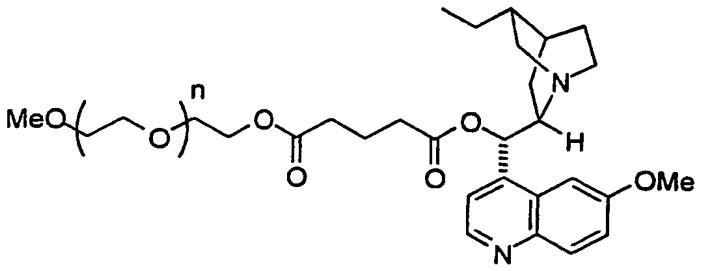


and

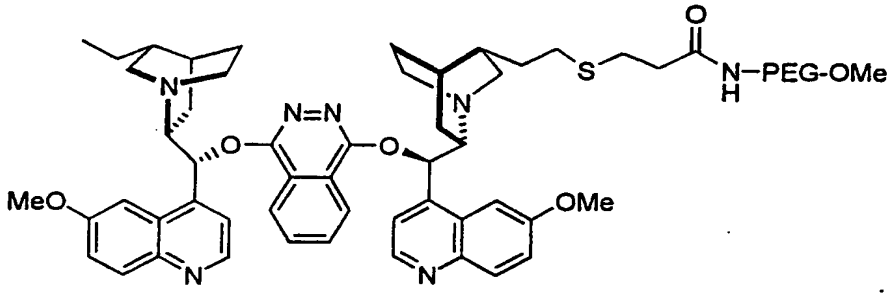


In a preferred embodiment, the above alkaloid ligands are coupled to said polyethylene glycol by a linkage selected from the group consisting of ester linkage, amide linkage, thoester linkage, ester linkage, thiether linkage, and sulphone linkage. Preferred examples of the PEG bound alkaloid ligand are represented by the following structures:





and



Another aspect of the invetnion is directed to an improved process for catalyzing a hydroxylation reaction. The process is of the type which includes a step for admixing, within a reaction medium, an olefin, an oxidizing agent, a catalyst for catalyzing the hydroxylation reaction, and an alkaloid ligand for accelerating the catalysis of the hydroxylation reaction. The process is improved by the use of a PEG bound alkaloid ligand. The PEG bound alkaloid ligand is soluble in the reaction medium and precipitable in a precipitation medium. In a preferred embodiment, the hydroxylation reactions are asymmetric dihydroxylation reaction and the PEG bound alkaloid ligand is chiral. A preferred oxidizing agent is a mixture which includes $K_3Fe(CN)_6$ (potassium ferricyanide III), $CH_3SO_2NH_2$

(methanesulfonamide), OsO_4 and K_2CO_3 (potassium carbonate). Another preferred oxidizing agent is a mixture which includes methylmorpholine *N*-oxide (NMO), tetraethylammonium acetate tetrahydrate, and OsO_4. The preferred catalyst is OsO_4. Preferred reaction media are acetone/water or butanol/water. Preferred precipitation media include the addition of diethyl ether or cold ethanol to the reaction media.

Another aspect of the invention is directed to a process for catalyzing an hydroxylation reaction. In the first step of this process, an olefin, an oxidizing agent, a catalyst for catalyzing the hydroxylation reaction, and an alkaloid ligand for accelerating the catalysis of the hydroxylation reaction are admixed in a reaction medium. The admixture occurs in a reaction medium under reaction conditions for producing an hydroxylation product. In the second step, a precipitation medium is admixed with the reaction medium of the first step for precipitating the PEG bound alkaloid ligand. In the third step, the precipitated PEG bound alkaloid ligand of the second step is separated from the hydroxylation product so as to recover the PEG bound alkaloid ligand. In a preferred mode, the hydroxylation reaction in the first step is an asymmetric dihydroxylation reaction and the PEG bound alkaloid ligand is chiral.

Another aspect of the invention is directed to a further process for catalyzing an hydroxylation reaction. In the first step of this process, one or more reactants are admixed with a catalyst for catalyzing the hydroxylation reaction and with a PEG bound alkaloid ligand for accelerating the catalysis of the hydroxylation reaction. The admixture occurs occurs in a reaction medium under reaction conditions for producing an hydroxylation product, In the second step,

a precipitation medium is admixed the reaction medium of of the first step for precipitating the PEG bound alkaloid ligand. In the third step, the hydroxylation product of the second step is separated B from the precipitated PEG bound alkaloid ligand for obtaing purified product. In a preferred mode, the hydroxylation reaction is an asymmetric dihydroxylation reaction and the PEG bound alkaloid ligand is chiral.

Brief Description of Figures:

Figure 1 illustrates a prior art alkaloid ligand, i.e. compound 1, a PEG radical, i.e., compound 4, alkaloid ligand coupled to a linkage unit, i.e. compound 3, and a PEG bound alkaloid ligand, i.e., compound 2.

Figure 2 illustrates the synthesis of ligands 2 and 3 with the following conditions: (a) TEA, DMAP, glutaric anhydride (60 %); (b) DCC, DMAP, ROH (95 %).

Figure 3 illustrates the comparison of catalytic asymmetric hydroxylations using compound 1-4. The indicated notations are as follows: (a) see Petri et al. *Chirality* **1995**, *7*, 580 for experimental details; (b) results from Petri et al. *Chirality* **1995**, *7*, 580; ligand 2, which was recovered from entry 3, was recycled a total of four times; (d) for the purpose of comparison, the reaction was stopped after 5 hours (e) slow addition time of olefin.

Figure 4 illustrates polymer-bound *trans*-cinnamate esters 7-11 for the Sharpless AD reaction.

Figure 5 illustrates the reaction in which trans-cinnamic acid was immobilized to the four polymeric supports 7-11 (figure 4) and the reactivity of 7-11 was

demonstrated by using the ligands **13** and **14** for the Sharpless AD reaction.

Figure 6 tabulates various AD reactions conducted upon various polymer bound *trans*-cinnamate esters using the ligands **13** and **14**. The indicated notations are as follows: [a] OsO_4 equivalents realtive to olefin. [ligand]/[OsO_4] = 2.5. [b] Method A: $K_3Fe(CN)_6$ and *t*-butanol/water = 1/1 system at room temperature. Method B: *N*-methylmorpholine-*N*-oxide and acetone/water = 10/1 system at 4°C. [c] Determined from the ratio of diol proton signals to the remaining olefin signals by NMR. [d] Determined through NMR analysis of the derived *bis*-Mosher ester of the diol.

Figure 7 illustrates the chemical synthesis of ligands **20** and **14**.

Figure 8 tabulates various catalytic Asymmetric Dihydroxylation Reactions using Ligand **14**. The indicated notations are as follows: (a) For NMO system, the molar ratio of olefin/OsO_4/ligand = 1/0.04/0.1, and for $K_3Fe(CN)_6$ system, the molar ratio was 1/0.005/0.1. (b) Number in parenthesis represents results for a free ligand $(DHQD)_2PHAL$ from Sharpless et al. *J. Org. Chem.* **1992**, *57*, 2768.

Detailed Description of the Invention

The invention is directed to the synthesis and use of polyethylene glycol monomethyl ether-bound cinchona alkaloid ligands in the ligand-accelerated catalytic (LAC) Sharpless asymmetric dihydroxylation reaction (AD) with a range of olefins.

Example 1. Synthesis and Exemplary use of Polyethylene glycol monomethyl ether-bound cinchona alkaloid ligands in the AD reaction

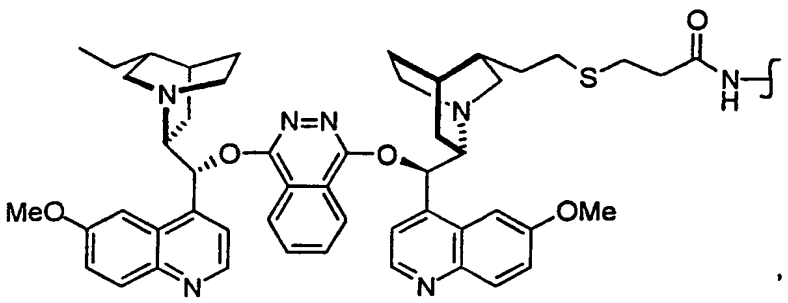
The following examples are exemplary conditions which demonstrate the versatility of the methodology and are not meant to be restrictive with the models disclosed. Rather, the methodology can be used with symmetrical, nonsymmetrical, substituted and unsubstituted - primary, secondary or tertiary olefins. In addition, other commercially available alkaloid ligands can be used in lieu of the disclosed dihydroquinidine hydrochloride 5 (Figure 2). Preferred alkaloid ligands include the following:

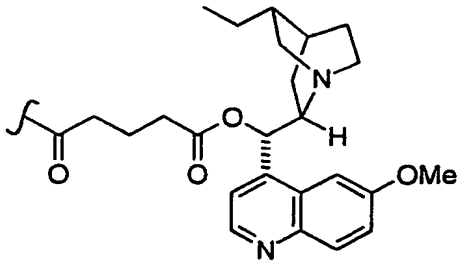
1. from U.S. Patent No. 5,260,461, incorporated herein by reference:
   1,4-bis-(9'-O-dihydroquinidyl)-phthalazine;
   1,4-bis-(9'-O-quinidyl)-phthalazine;
   3,6-bis-(9'-O-dihydroquinidyl)-pyridazine;
   3,6-bis-(9'-O-quinidyl)-pyridazine; 1,4-bis-(9'-O-dihydroquinyl)-phthalazine;
   1,4-bis-(9'-O-quinyl)-phthalazine;
   3,6-bis-(9'-O-dihydroquinyl)-pyridazine;
   3,6-bis-(9'-O-quinyl)-pyridazine;
2. from U.S. Patent No. 4,871,855, incorporated herein by reference:
   dimethylcarbamoyl dihydroquinidine;
   benzoyl dihydroquinidine;
   4-methoxybenzoyl dihydroquinidine;

4-chlorobenzoyl dihydroquinidine;
2-chlorobenzoyl dihydroquinidine;
4-nitrobenzoyl dihydroquinidine;
3-chlorobenzoyl dihydroquinidine;
2-methoxybenzoyl dihydroquinidine;
3-methoxybenzoyl dihydroquinidine;
2-naphthoyl-dihydroquinidine;
cyclohexanoyl dihydroquinidine;
p-phenylbenzoyl dihydroquinidine;
dimethylcarbamoyl dihydroquinidine;
benzoyl dihydroquinine;
4-methoxybenzoyl dihydroquinine;
4-chlorobenzoyl dihydroquinine;
2-chlorobenzoyl dihydroquinine;
4-nitrobenzoyl dihydroquinine;
3-chlorobenzoyl dihydroquinine;
2-methoxybenzoyl dihydroquinine;
3-methoxybenzoyl dihydroquinine;
2-naphthoyl dihydroquinine;
cyclohexanoyl dihydroquinine;
p-phenylbenzoyl dihydroiquinone;

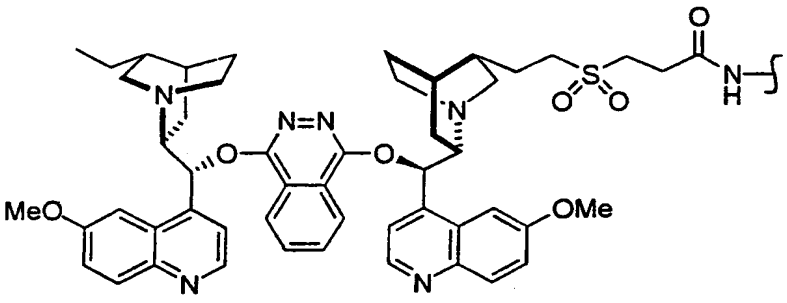
3. From U.S. Patent No. 5,126,494, incorporated herein by reference:

acrylonitrile co-polymer of 9-(4-chlorobenoyloxy)-quinidine;
acrylonitrile co-polymer of 11-((2-acryloyloxy)ethyl-sulfinyl)-9-(4-chlorobenoyloxy)-10,11-dihydroquinidine;
acrylonitrile co-polymer of 11-[2-acryloyloxy)ethylsulfonyl]-9-(N,N-dimethylcarbamoyl)-10,11-dihydroquinidine;
acrylonitrile co-polymer of 9-(10-undecanoyl)-10,11-dihydroquinidine; and
alkaloid ligands represented by the following structures:





and



Reaction conditions which cover temperature, substrate equivalents, reaction time(s), work-up(s) and buffer solutions (pH levels) may vary, depending on the substrate used, however all proportions are approximately the same. A representative procedure is

provided in the synthetic protocals.

In an effort to circumvent the problems observed with insoluble supports and LAC, yet, provide the economical and physical advantages (product isolation and reagent recovery) that a polymeric support can offer, we have developed the soluble homopolymer MeO-PEG as a suitable scaffold for the AD reaction. The synthesis of polyethylene glycol monomethyl ether bound cinchona alkaloid ligands (Figure 1) and their successful use in the LAC asymmetric dihydoxylation reaction of various olefins is described as follows.

The synthesis of the MeO-PEG-bound dihydroquinidine ligands is depicted in Figure 2. The commercially available hydroquinidine **5** (Aldrich) was acylated using glutaric anhydride and 4-*N,N'*-dimethylaminopyridine (DMAP) to provide carboxylic acid **6**. This reaction, though simple, provides the linking unit necessary for attachment to the homopolymer MeO-PEG or any other amino or alcohol group. The coupling of acid **6** to polyethylene glycol monomethyl ether and ethyl alcohol in the presence of dicyclohexylcarbodiimide and DMAP produced the homopolymer **2** and its simple diester homologue **3** respectively.

The chiral homopolymer **2** was the archetype used to examine and compare all of the AD reactions investigated. The structural similaritiy of **2** to the insoluble acrylonitrile ligand **1**, allowed for a direct comparison between soluble and insoluble supports to be made (Kim et al. Tetrahedron Lett. 1990, 31, 3003) while contrasting the reactivity of ligands **2**, **3**, and **4** in the AD reaction would delineate any effect that the polyethylene glycol backbone may have on asymmetric induction. In addition, to standardize the comparisons between our soluble ligand support and the insoluble

ligand support, we us d the same conditions as reported for the ligand 1- AD catalytic reaction (Kim et. al. Tetrahedron Lett. 1990, 31, 3003).

The MeO-PEG-supported catalyst 2 is completely soluble in an acetone-water mixture (v/v = 9/1); thus the catalytic reaction is completely homogeneous. Of greater note is that the reaction is complete within the same time frame as that of its solution counterpart with no decrease of yields or enantioselectivity as tablutated in Figure 3. For this methodology to be useful, product isolation, separation, and recovery of the polymer bound ligand must be straightforward and reliable. Upon completion of the AD reaction, the entire mixture was diluted with methylene chloride, dried (anhydrous sodium sulfate) and filtered. Diethyl ether was added to the resulting mixture in order to precipitate MeO-PEG-bound ligand (typically, the MeO-PEG-bound ligand was recovered in >98 % yield). The filtrate contained the dihydroxylated product.

The asymmetric dihydroxylation of a variety olefins by ligands 1-4 is shown in Figure 3. Immediately evident is the fact that MeO-PEG-bound ligand 2 is more efficient than the insoluble polymer bound ligand 1 (Kim et. al. Tetrahedron Lett. 1990, 31, 3003), both in its enantioselectivity and reactivity (entries 1 and 2 , Figure 3). What is more, the polymer-bound ligand 2 is easily recovered in near quantitative fashion and recycled several times with no loss of reaction yield or enantioselectivity (entry 3, Figure 3). With all four olefins tested, MeO-PEG-bound ligand 2 was as effective as free ligand 3 (compare entries 2 and 4, entries 6 and 7, entries 8 and 9, and entries 10 and 11). These findings strongly suggest that the MeO-PEG back-bone does not influence or affect the observ d asymmetric induction (entry 5). Furthermore, these findings

provide direct support for our notion that for successful polymer-bound LAC all components involved in the reaction must be able to interact freely with each other in solution.

In summary, a process has been invented which demonstrates how a chiral ligand can be integrated into a soluble polymeric species so that LAC can operate in an unhindered manner on a polymer support. The soluble polymer-bound ligand provides all the advantages that an insoluble support can offer, while also being as effective as a free ligand both in reactivity and selectivity. This new soluble polymer bound-ligand system should be applicable to other classes of AD ligands for improved enantioselectivity (Kolb et al. Chem. Rev. 1994, 116, 2483) as well as other enantioselective catalytic processes (Takaya et al. J. Am. Chem. Soc. 1987, 109, 1596; Zhang et al. J. Am. Chem. Soc. 1990, 112, 2801; Lowenthal et al. Tetrahedron Lett. 1991, 32, 7373; Li et al. J. Am. Chem. Soc. 1993, 115, 5326; Evans et al. J. Am. Chem. Soc. 1993, 115, 5328; Johnson et al. in Catalytic Asymmetric Synthesis Ed.; VCH: Weinheim, 1993; pp. 103-158; Jacobsen et al. in Catalytic Asymmetric Synthesis; Ojima, I. Ed.; VCH: Weinheim, 1993; pp. 159-202; Li et al. Angew. Chem., Int. Ed. Engl. 1996, 35, 451).

The MeO-PEG polymer will not only be useful to the research chemist but also for effecting the separation of catalyst from product in homogeneous industrial applications (Steckhan et al. Angew. Chem. Int. Ed. Engl. 1990, 29, 388; Herrmann et al. Angew. Chem. Int. Ed. Engl. 1993, 32, 1524; Bergbreiter et al. J. Am. Chem. Soc. 1993, 115, 9295; Horvath et al. Science 1994, 266, 72). Finally because of its desirable physical properties, this and other ligand accelerated catalysts that are incorporated within liquid phase supports may

find use in automated high through-put synthetic efforts (Frisbee et al. J. Am. Chem. Soc. 1984, 106, 7143; Sabadosa et al. Lab. Rob. Automation 1989, 1, 265; Dewitt et al. Current Opin. Biotech. 1995, 6, 640).

Example 2. Synthesis and Exemplary use of attachment of small organic olefinic moiety to various polymeric matrixs with the Sharpless AD reaction

Since the initial discovery of Merrifield (Merrifield et al. *J. Am. Chem. Soc.* **1963**. 85. 2149-2154) concerning the synthesis of oligopeptides the use of polymers as supports, reagents or even catalysts, for various syntheses mostly related to fine chemistry has increased (Crowley et al. *Acc. Chem. Res.* **1976**, 9, 135-144; Leznoff et al. *Acc. Chem. Res.* **1978**, 11, 327-333; Manecke et al. *Angew. Chem. Int. Ed. Engl.* **1978**, 17, 657-670; Frechet *Tetrahedron* **1981**, 37, 663-688). Recently, a high level of activity has been devoted to the field due to the application of combinatorics to the drug discovery arena (*Molecular Diversity and Combinatorial Chemistry* (eds.: I.M. Chaiken and K.D. Janda) American Chemical Society, Washington, D.C., 1996; Fruchtel et al. *Angew. Chem. Int. ed. Engl.* **1996**, 35, 17-42; Balkenhohl et al. *Angew. Chem. Int. ed. Engl.* **1996**, 35, 2288-2337). Although a resurgence of interest in polymers for organic synthesis has been seen, little effort has been paid to the structural parameters of the supports. This being most evident in the realm of automation of organic synthesis.

In an effort to delineate the shortcomings of insoluble polymer bound ligand-accelerated catalysis (LAC), we show how a chiral ligand can be integrated onto a soluble polymeric species so that LAC can operate in an unhindered manner on a polymer support (Han et al. *J. Am. Chem. Soc.* **1996**, 118, 7632-7633). However, the

converse wherein a small organic moiety is attached to a polymeric matrix and the polymer's influence on the LAC reaction has yet to be investigated. Implications from the successful combination of these two scenario's being that a multipolymer LAC reaction maybe a feasiable target. In this context, we have collected data using both solid and liquid phase polymers to evaluate the influence of the support structure on the Sharpless asymmetric dihydroxylation (AD) reaction. The outgrowth of these findings have allowed us to successfully run a multipolymer Sharpless AD reaction.

A variety of supports have been recently engaged in organic synthesis (Terrett et al. *Tetrahedron* **1995**, 51, 8135-8173; Thompson et al. *Chem. Rev.* **1996**, 555-600; Hermkens et al. *Tetrahedron* **1996**, 52, 4527-4554). Typically, they may be grouped into three categories. (1) Minimal cross-linked supports that form well solvated gels (R.B. Merrifield, *Angew. Chem. Int. Ed. Engl.* **1985**, 24, 799-810); (2) Porous but rigid supports with a high degree of cross linking (Bartholin et al. *Prog. Polym. Sci.* **1982**, 8, 277-332); (3) Linear soluble polymers also known as liquid phase supports (Geckeler et al. in *Advances in Polymer Science*, Vol. 121 (Eds. Spring-Verlag, Berlin, 1995, p. 31; Bayer et al. , *Angew. Chem. Int. Ed. Engl.* **1991**, 30, 113-129; Bergbreiter in *Proceedings of the Sixth Annual IUCCP Symposium on Functional Polymers*. (Eds. D.E. Bergbreiter and C.R. Martin) Plenum Press, New York, 1989, p. 143. Two low divinyl benzene-cross-linked polystyrene beads (Merrifield and Wang resin) and the graft copolymer polystyrene-polyethylene glycol (Tentagel) were utilized as category-1 supports. The choice of these resins was based on their fundamental differences. Merrifield and Wang resins are relatively hydrophobic matrices while Tentagel is considered to be a hydrophilic tentacle polymer with more "solution-like" characteristics. The

category-3 support used was polyethylene glycol (PEG). Besides it fulfilling the criteria of a group-3 polymer, this homopolymer was enlisted as it contrasted the chemical reactivity differences between PEG and Tentagel.

Trans-cinnamic acid was immobilized to the four polymeric supports (Figure 4). Using this format insured that all supports would have an olefin tethered as an ester with the composition of the polymer determining the overall reactivity. Furthermore, because the reactivity of ethyl *trans*-cinnamate (**11**) is a documented substrate for the AD reaction using the ligand 1,4-phthalazinediyldiether hydroquinidine [$(DHQD)_2PHAL$, **14**, Figure 5] Sharpless et al. *Org. Chem.* **1992**, 57, 2768-2771, a direct correlation could be made between solution and polymeric reactions.

Figure 6 shows that the resins structural make-up is the dominant factor influencing the AD reaction. Overall the amount of metal/ligand used, reaction time required for product conversion, and enantiomeric excess observed varies greatly depending on the support. Contrasting all four polymeric supports in terms of the AD reaction clearly shows that the non-cross-linked liquid phase resin **10** (entries 6 and 10; Figure 6) provides the best overall results when considering reaction time, conversion percent, enantiomeric excess and metal/ligand ratio. Furthermore, this soluble polymer substrate compares favorably with entry 11 which details our findings for the matrix removed olefin counterpart **11**.

Specifically looking at the three insoluble supports Tentagel-**9** out performed the Wang-**8** and Merrifield-**7** resins in the optimum enantioselective oxident, potassium ferricyanide (entries 1-5). However,

the cross-linked polystyr ne suppports-**8/9**, can provide a suitable environment for LAC when NMO is applied as the oxident and acetone/water is the solvent (entries 7 and 8). It may have been anticipated that supports **7** and **8** would show an overall inability to support the AD reaction in the potassium ferricyanide oxident system as these polymers have rather modest swelling properties in the solvent system employed. The consequences of poor swelling would include limited chain mobility which could compromise the location and distribution of catalyst to olefin within these matrices.

Somewhat unexpected was the large amount of metal and ligand that was required for the Tentagel resin-**9** to provide a respectable reaction time, conversion and enantioselec-tivity (compare entries 3,4, and 5). Interestingly there appears to be a threshold of catalyst that is required with Tentagel for any conversion to diol be seen (compare entries 3 and 4). We investigated this aspect further through the following two experiments. In one reaction conditions as detailed in entry 4 were utilized. After 24h fresh unbound olefin **11** (0.125 mmol.) was added to the reaction mixture as was OsO_4 (0.02 eq.relative to the olefin), K_2CO_3 (3.0 eq relative to the olefin), and $K_3Fe(CN)_6$ (3.0 eq relative to the olefin). The reaction mixture was analyzed after 10h and was found to have only obtained 10% conversion of **11** to **12b**. In the second reaction unbound olefin **11** was used throughout the same sequence of events, however, in this scenario recharging the reaction mixture with **11** provided complete conversion to **12b** in 2.5h. Such results suggest that free ligand becomes entangled in the insoluble support limiting its availability. Thus, while resin-**9** is a more hydrophilic copolymer than resins-**7** and **8** it still must be considered a "quasi-homgeneous" matrix which is subject to some of the same limitations found

within insoluble resins.

In our defining of the influence of the structure and support texture on the kinetics and enantioselectivty of the AD reaction (vide supra) we identified that a correct combination of soluble and insoluble polymers (i.e. a multipolymeric reaction) could in principle make a tenable AD process. The use of more than a single polymeric reagent/catalyst in reactions either simultaneously or consecutively has been accomplished, but its exploitation has been limited to date (Examples in the area of peptide syntheses include: a) G. Heusel, G. Bovermann, W. Göhring, G. Jung, *Angew. Chem. Int. Ed. Engl.* **1977**, 16, 642-643. b) H. Frank, H. Hagenmaier, *Experentia* **1975**, 31, 131-133. For examples other than peptides see: a) B.J. Cohen, M.A. Kraus, A. Patchornik, *J. Am. Chem. Soc.* **1977**, 99, 4165-4167. b) C.V. Pittman, L.R. Smith, *J. Am. Chem. Soc.* **1975**, 97, 1749-1754 c) J.P. Collman, K.M. Kosydar, M. Bressan, W. Lamanna, T. Garrett, *J. Am. Chem. Soc.* **1984**, 106, 2569-2579. d) D.E. Bergbreiter, R. chandran, *J. Am. Chem. Soc.* **1987**, 109, 174-179. e) D. E. Bergbreiter, R. Chandran, *J. Am. Chem. Soc* **1985**, 107, 4792-4793. f) J. J. Parlow, *Tet. Lett.* **1995**, 36, 1395-1396. g) F. Svec, J. M. J. Frechet, *Science* **1996**, 273, 205-211. For the detection of highly reactive intermediates using two polymeric reagents simultaneous "Three phase text", see J. Rebek *Tetrahedron*, **1979**, 35, 723-731 and references cited therein). The combination of Tentagel resin-**9** and MeO-PEG-[$(DHQD)_2PHAL$] **14**, (Figure 5) was investigated as the multipolymer components. Entry 12 shows that this combination of polymers can successfully support LAC. These two polymers are physically quite different, yet, the outgrowth of this methodology translates into facile product separation and ligand re-isolation. The significance of such technology should have direct application to the

automation of synthetic processes (Frisbee et al. *J. Am. Chem. Soc.* **1984**, 106, 7143-7145. b) Dewitt et al. *Curr. Biol.*, **1995**, 6, 640-645. c) Kramer et al. *Chemtech* **1989**, 19, 682-688. d) Hobbs Dewitt et al. *Acc. Chem. Res.* **1996**, 29, 114-122).

From the literature (Terrett et al. *Tetrahedron* **1995**, 51, 8135-8173; Thompson et al. *Chem. Rev.* **1996**, 555-600; Hermkens et al. *Tetrahedron* **1996**, 52, 4527-4554) as well as from the results reported here a few guidelines seem to be emerging concerning the influence of the structure and support texture on the kinetics and selectivity of polymer supported organic reactions. These lines appear valid for both supported catalysts as well as for organic moieties attached to these matrices. The key in the context of both systems can be assimilated back to properties inherent to all polymers: Accessibility or lack of, and microenvironment, the latter often being a prerequisite for the first.

In the field of small molecule combinatorics example 2 demonstrates that multipolymeric reactions should be applicable in the automation of organic synthesis.

Example 3: PEG Approach to the Sharpless Catalytic Asymmetric Dihydroxylation (AD) using a [(DHQD)2PHAL-PEG-OMe] Ligand.

In an effort to circumvent the problems associated with heterogeneous reactions, we illustrate in example 1 (vida supra) a homogeneous extention to the AD reaction using a soluble polymer, poly(ethylene glycol) mono-methyl ether (MeO-PEG), bound cinchona alkaloid ligand (Han et al. *J. Am. Chem. Soc.* **1996**, *118*, 7633). This liquid-phase methodology (Han et al. *J. Am. Chem. Soc.* **1996**, *118*, 2539; Han et al. *Methods in Enzymology* **1996**, *267*, 234; Han et al. *Proc. Natl. Acad. Sci. USA* **1995**,

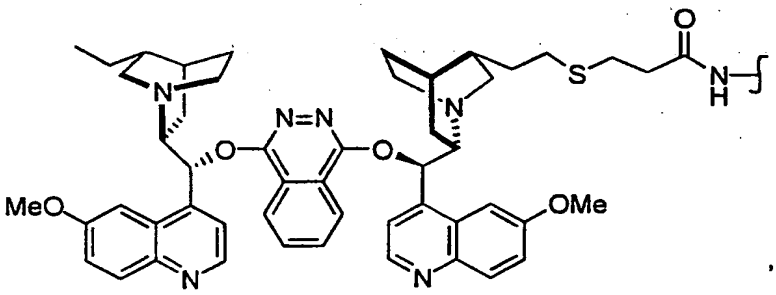
92, 6419) provided all of the advantages that an insoluble polymer has to offer, while also being as effective as the free ligand in terms of both reactivity and enantioselectivity. However, the ligand 5 (Figure 2) utilized was not the most effective in terms of enantioselectivity and reactivity for the solution-phase AD reaction. Therefore in an attempt to improve our liquid-phase approach to the AD reaction we illustrate in this example the synthesis of a $(DHQD)_2PHAL$ ligand bound to MeO-PEG-NH_2 and its successful use in the AD reaction of various olefins (Figures 7 and 8). Furthermore, we extend the methodology to include additional ligands which, when bound to the PEG polymer, afford successful use in the AD reaction. The additional ligands include the following alkaloid ligands:

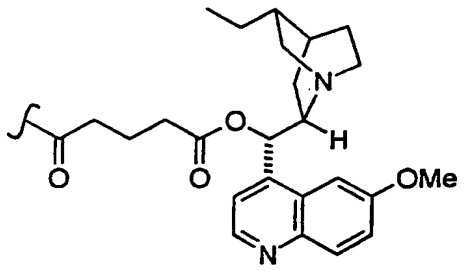
1. from U.S. Patent No. 5,260,461, incorporated herein by reference:
   1,4-bis-(9'-O-dihydroquinidyl)-phthalazine;
   1,4-bis-(9'-O-quinidyl)-phthalazine;
   3,6-bis-(9'-O-dihydroquinidyl)-pyridazine;
   3,6-bis-(9'-O-quinidyl)-pyridazine; 1,4-bis-(9'-O-dihydroquinyl)-phthalazine;
   1,4-bis-(9'-O-quinyl)-phthalazine;
   3,6-bis-(9'-O-dihydroquinyl)-pyridazine;
   3,6-bis-(9'-O-quinyl)-pyridazine;
2. from U.S. Patent No. 4,871,855, incorporated herein by reference:
   dimethylcarbamoyl dihydroquinidine;
   benzoyl dihydroquinidine;
   4-methoxybenzoyl dihydroquinidine;
   4-chlorobenzoyl dihydroquinidine;
   2-chlorobenzoyl dihydroquinidine;
   4-nitrobenzoyl dihydroquinidine;
   3-chlorobenzoyl dihydroquinidine;
   2-methoxybenzoyl dihydroquinidine;
   3-methoxybenzoyl dihydroquinidine;

2-naphthoyl-dihydroquinidine;
cyclohexanoyl dihydroquinidine;
p-phenylbenzoyl dihydroquinidine;
dimethylcarbamoyl dihydroquinidine;
benzoyl dihydroquinine;
4-methoxybenzoyl dihydroquinine;
4-chlorobenzoyl dihydroquinine;
2-chlorobenzoyl dihydroquinine;
4-nitrobenzoyl dihydroquinine;
3-chlorobenzoyl dihydroquinine;
2-methoxybenzoyl dihydroquinine;
3-methoxybenzoyl dihydroquinine;
2-naphthoyl dihydroquinine;
cyclohexanoyl dihydroquinine;
p-phenylbenzoyl dihydroiquinone;

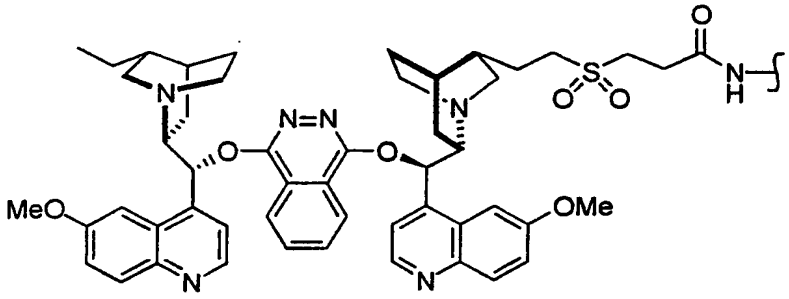
3. From U.S. Patent No. 5,126,494, incorporated herein by reference:

acrylonitrile co-polymer of 9-(4-chlorobenoyloxy)-quinidine;
acrylonitrile co-polymer of 11-((2-acryloyloxy)ethyl-sulfinyl)-9-(4-chlorobenoyloxy)-10,11-dihydroquinidine;
acrylonitrile co-polymer of 11-[2-acryloyloxy)ethylsulfonyl]-9-(N,N-dimethylcarbamoyl)-10,11-dihydroquinidine;
acrylonitrile co-polymer of 9-(10-undecanoyl)-10,11-dihydroquinidine; and
alkaloid ligands represented by the following structures:





and



The five step synthetic route to **14** is outlined in Figure 7. In the first step, a mixture of dihydroquinidine, 1,4-dichlorophthalazine, KOH, and K_2CO_3 in dry toluene are refluxed, with a concurrent azeotropic removal of water, to give the mono-substituted chlorophthalazine **17** which upon similar transformation with quinidine provided the di-substituted phthalazine **18** (Amberg et al. *J. Org. Chem.* **1993**, *58*, 844; Lohray et al. *Tet. Lett.* **1994**, *35*, 6559). The heating of **18** and 3-mercaptopropionic acid (3-MPA) in the presence of 2,2'-azobisisobutyronitrile (AIBN) in benzene (70 °C) allowed the isolation of **19** as a tan precipitate (Inagaki et al. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4121). The acid **19** was coupled to MeO-PEG-NH2 in

the presence of N,N- dimethylaminopyridine (DMAP) and 1,3-dicyclohexylcarbodiimide (DCC) in methylene chloride (DCM) (Pillai et al. *J. Org. Chem.* **1980**, *45*, 5364). After the reaction was complete, the insoluble urea side-product was removed by filtration and the pegylated ligand **20** was isolated from the reaction mixture by precipitation following a slow addition of diethyl ether. The sulfide **20** was oxidized to the desired sulfone **14** by a mixture of OsO_4/*N*-methylmorpholine-*N*-oxide (NMO) [in acetone/water (v/v, 2/1)] (Kaldor et al. *Tetrahedron. Lett.* **1991**, *32*, 5043).

Ligand **14** was completely soluble either in *t*-butanol/water or acetone/water solvent systems allowing the study of homogeneous AD reactions. The AD reaction results of **14** with various olefins are shown in Figure 8 and a number of features are noteworthy. First, it is evident that the *t*-Butanol/water solvent produces considerably higher *ees* for all olefins tested consistent with previous reports (Pini et al. *Tetrahedron Lett.* **1991**, *32*, 5175; Lohray et al. *Tetrahedron Lett.* **1992**, *33*, 5453.; Pini et al. *Tetrahedron: Asymmetry* **1993**, *4*, 2351; Lohray et al. *Tetrahedron Lett.* **1994**, *35*, 6559; Pini et al. *Tetrahedron* **1994**, *50*, 11321; Pini et al. *Tetrahedron Lett.* **1995**, *36*, 1549; Sung et al. *Tetrahedron: Asymmetry* **1995**, *6*, 2687; Petri et al. *Chirality* **1995**, *7*, 580; Song et al. *Tetrahedron: Asymmetry* **1996**, *7*, 645). Second, in terms of both reaction time and enantioselectivity, ligand **14** accelerated AD reactions are comparable to its free ligand counterpart, strongly suggesting that the MeO-PEG backbone does not adversely alter either asymmetric induction or the rate of formation of the osmium-ligand-olefin ternary complex. Finally, the ligand **14** can be isolated in virtually quantitative yield by precipitation using diethyl ether (Han et al. *J. Am. Chem. Soc.* **1996**, *118*, 7633).

Combined with our previous example 1 (vida supra: Han et al. *J. Am. Chem. Soc.* **1996**, *118*, 7633), the present results demonstrate that MeO-PEG bound ligands behave in a similar fashion to unimmoblized ligands in the AD reaction. What makes this finding even more impressive is that this soluble polymer approach provides the added convenience of ligand recovery and product isolation.

Synthetic Protocals

General. Methylene chloride and methanol were dried over CaH_2 and powdered magnesium respectively. Polyethylene glycol monomethyl ether (MeO-PEG, MW. = 5000) was purchased from Aldrich and was dried over P_2O_5 under vacuum before use. All other solvents and chemicals were obtained from commercial sources, and were used without further purification, unless otherwise stated. NMR spectra were obtained on a Bruker AM-300 spectrometer.

Synthesis of Dihydroquinidine Glutarate (Mono-ester) 6 as illustrated in Figure 2. Dihydroquinidine hydrochloride 5 (0.500 g, 1.38 mmol; Aldrich) dissolved in methylene chloride was neutralized by the slow addition of triethylamine (0.140 g, 1.38 mmol) at 4 °C. This was followed by the addition of 4-(*N,N'*-dimethyl)aminopyridine (0.170 g, 1.39 mmol) in methylene chloride. To this reaction mixture was slowly added glutaric anhydride (0.315 g, 2.76 mmol). The reaction temperature was raised to room temperature, and the reaction mixture was stirred for an additional 2 h. All volatiles were removed in vacuo, and the resulting residue was purified by column chromatography (silica-gel, methylene chloride: methanol = 9: 1). The dihydroquinidine glutarate (mono-ester) was obtained as a white foam (0.364 g, 60.0 %): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.95 (t, J = 7 Hz, 3H), 1.35 (m, 1H), 1.5-2.1 (m, 9H), 2.2-2.7 (m, 5H), 3.13 (q, J = 7 Hz, 1H), 3.2-3.6 (m,

3H), 4.11 (s, 3H), 7.28 (d, J = 3 Hz, 1H), 7.40 (dd, J = 9, 3 Hz, 1H), 7.43 (s, 1H), 7.72 (d, J = 4 Hz, 1H), 8.03 (d, J = 9 Hz, 1H), 8.69 (d, J = 4 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 11.8, 20.1, 21.7, 24.3, 25.5, 26.2, 34.2, 34.4, 35.9, 50.5, 51.2, 57.4, 59.3, 71.5, 102.4, 119.2, 124.2, 127.2, 131.6, 143.0, 144.8, 148.0, 160.4, 172.5, 177.3; HRMS (FAB) calcd for [$C_{25}H_{32}N_2O_5$ + H^+] 441.2389, found 441.2375.

Synthesis of Ethyl, dihydroquinidine glutarate 3 as illustrated in Figure 2. 1,3-Dicyclohexylcarbodiimide (DCC, 0.153 g, 0.742 mmol) was added to a mixture of absolute ethanol (0.0113 g, 0.245 mmol), DMAP (0.0150 g, 0.123 mmol), and the dihydroquinidine glutarate (mono-ester) **6** (0.324 g, 0.736 mmol) in methylene chloride. The reaction mixture was stirred until the dihydroquinidine glutarate (mono-ester) **6** disappeared as determined by thin layer chromatography (TLC; the reaction typically took approximately 3 h). The reaction mixture was filtered through celite to allow removal of urea precipitate, and the product was isolated after evaporation of the solvent. The residue was purified by column chromatography (methylenechloride: methanol = 9: 1) to give **3** (0.109 g, 95.1 %): ^{1}H-NMR (300 MHz, $CDCl_3$) d 0.87 (t, J = 7 Hz, 3H), 1.35 (m, 1H), 1.16 (t, J = 7 Hz, 3 H), 1.3-1.6 (m, 7H), 1.75-2.00 (m, 3H), 2.43 (t, J = 7 Hz, 2H), 2.6-3.0 (m, 3H), 3.24 (q, J = 7 Hz, 1H), 3.92 (s, 3H), 4.05 (q, J = 7 Hz, 2H), 6.62 (d, J = 7 Hz, 1H), 7.26 (d, J = 3 Hz, 1H), 7.32 (dd, J = 9, 3 Hz, 1H), 7.42 (d, J = 4 Hz, 1H), 7.93 (d, J = 9 Hz, 1H), 8.69 (d, J = 4 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) d 11.7, 14.1, 19.9, 22.3, 25.2, 25.7, 26.3, 33.0, 33.2, 36.6, 49.6, 50.3, 55.9, 58.7, 60.3, 72.7, 101.1, 118.0, 122.1, 126.6, 131.6, 143.1, 144.5, 147.1, 158.1, 171.4, 172.7; HRMS (FAB) calcd. for [$C_{27}H_{36}N_2O_5$ + H^+] 469.2702, found 441.2718.

Synthesis of p lyethylene glycol, dihydroquinidine glutarate 2 as illustrated in Figure 2. DCC (0.153 g,

0.742 mmol) was added to a mixture of polyethylene glycol (1.23 g, 0.246 mmol), DMAP (0.0150 g, 0.123 mmol), and dihydroquinidine glutarate (mono-ester) **6** (0.324 g, 0.736 mmol) in methylene chloride. The reaction mixture was stirred for 6 h and the urea precipitate was removed by filtration through celite. Diethyl ether was slowly added to the filtrate with a vigorous stirring, and a precipitate formed from was isolated as a white solid. This material was washed with absolute ethanol and diethyl ether, then dried over P_2O_5 *in vacuo* (1.29 g, 96.0 %). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.98 (t, J = 7 Hz, 3H), 1.40 (m, 1H), 1.6-2.7 (m, 17H), 3.11 (q, J = 7 Hz, 1H), 3.2-3.9 (polyethylene glycol peaks), 4.13 (s, 3H), 4.20 (t, J = 7 Hz, 2H), 7.23 (d, J = 3 Hz, 1H), 7.39 (dd, J = 9, 3 Hz, 1H), 7.59 (s, 1H), 7.80 (s, 1H), 8.05 (d, J = 9 Hz, 1H), 8.65 (d, J = 4 Hz, 1H).

Procedure for asymmetric dihydroxylation wherein representative substrates, product yields and ee's are tabulated in Figure 3. A small aliquot (catalytic amount) of OsO_4 in *t*-butanol (22 ml of OsO4 2.5 wt % solution) was added to a mixture of the polymer catalyst (0.300 g, 54.9 mmol), 4-methylmorpholine N-oxide (0.0386 g, 0.329 mmol), and tetraethylammonium acetate tetrahydrate (0.0574 g, 0.220 mmol) in acetone-water (10/1, v/v, 4 ml) at 4 °C. After stirring for 10 min, the olefin (4 eq. relative to the polymer ligand) was added either in one portion or by a slow addition. The reaction mixture was stirred at 4 °C until the olefin disappeared as judged by TLC. Next, solid sodium metabisulfate (0.500 g) was added, and the mixture was stirred for an additional 5 min, then diluted with methylene chloride (10 ml) and dried over Na_2SO_4. All solids were removed by filtration and washed three times with methylene chloride (3 x 5 ml). The combined filtrates were evaporated to half volume and diethyl ether was slowly added to the mixture under vigorous

stirring conditions. The precipitate obtained was collected on a glass filter, washed with absolute ethanol/ethyl ether, and dried in vacuo (0.294 g, 98 % recovery of ligand resulted from this procedure). Reduction in vacuo of the filtrate gave nearly pure dihydroxylated product. The enantiomeric excess of the diol was determined either by HPLC of the bis-acetate of hydrobenzoin on a Pirkle 1A ionic D-phenylglycine column or through NMR analysis of the derived bis-Mosher ester.

General Synthesis of Compounds 7 - 10 (as shown in Figure 4): *Trans*-cinnamic acid (1.1 equivalents; Aldrich) was coupled to each heterogeneous resin (1.0 equivalents) with the aide of EDC/DMAP coupling agents (1.2 equivalents EDC / 0.10 equivalents DMAP) in 0.10 Molar methylene chloride. For the soluble polymer MeO-PEG, a DCC/DMAP (1.2 equivalents EDC / 0.10 equivalents DMAP) combination was used for the preparation of **10**. Upon reaction completion (approximately 12 hours at 25 °C), the urea formed was removed by filtration. To the filtrate was added diethyl ether and **10** was separated as a white solid from the mixture. The loading of *trans*-cinnamic acid onto each polymer was determined to be >98 % by measuring the release of cinnamic acid and its methyl ester from the polymers with TFA/CH_2Cl (v/v, 95/5) and sodium methoxide in methanol respectively.

Procedure for asymmetric dihydroxylation for ol finic substrates attached to polymeric supports (example using polymer bound olefins) (Figures 5-6):

Method A:

A small aliquot of OsO_4 in *t*-butanol (OsO_4 2.5 wt % solution, see Figure 6 for the amount used in each reaction) was added to a mixture of the ligand (ligands **13** or **14** of Figure 5 or ligands **2** or **3** of Figure 2), $K_3Fe(CN)_6$ (0.250 g, 6 eq. relative to the olefin), K_2CO_3 (0.052 g, 3 eq.), and methanesulfonamide (0.012 g, 1 eq.) in *t*-butanol-water (1/1, v/v, 4 ml) at room temperature. Alternatively, the following ligands as described in the following U.S. Patents can be used in lieu of ligands **13**, **14**, **2**, or **3**:

1. from U.S. Patent No. 5,260,461, incorporated herein by reference:
   1,4-bis-(9'-O-dihydroquinidyl)-phthalazine;
   1,4-bis-(9'-O-quinidyl)-phthalazine;
   3,6-bis-(9'-O-dihydroquinidyl)-pyridazine;
   3,6-bis-(9'-O-quinidyl)-pyridazine; 1,4-bis-(9'-O-dihydroquinyl)-phthalazine;
   1,4-bis-(9'-O-quinyl)-phthalazine;
   3,6-bis-(9'-O-dihydroquinyl)-pyridazine;
   3,6-bis-(9'-O-quinyl)-pyridazine;
2. from U.S. Patent No. 4,871,855, incorporated herein by reference:
   dimethylcarbamoyl dihydroquinidine;
   benzoyl dihydroquinidine;
   4-methoxybenzoyl dihydroquinidine;
   4-chlorobenzoyl dihydroquinidine;
   2-chlorobenzoyl dihydroquinidine;
   4-nitrobenzoyl dihydroquinidine;
   3-chlorobenzoyl dihydroquinidine;
   2-methoxybenzoyl dihydroquinidine;
   3-methoxybenzoyl dihydroquinidine;
   2-naphthoyl-dihydroquinidine;

cyclohexanoyl dihydroquinidine;
p-phenylbenzoyl dihydroquinidine;
dimethylcarbamoyl dihydroquinidine;
benzoyl dihydroquinine;
4-methoxybenzoyl dihydroquinine;
4-chlorobenzoyl dihydroquinine;
2-chlorobenzoyl dihydroquinine;
4-nitrobenzoyl dihydroquinine;
3-chlorobenzoyl dihydroquinine;
2-methoxybenzoyl dihydroquinine;
3-methoxybenzoyl dihydroquinine;
2-naphthoyl dihydroquinine;
cyclohexanoyl dihydroquinine;
p-phenylbenzoyl dihydroiquinone;

3. From U.S. Patent No. 5,126,494, incorporated herein by reference:
acrylonitrile co-polymer of 9-(4-chlorobenoyloxy)-quinidine;
acrylonitrile co-polymer of 11-((2-acryloyloxy)ethyl-sulfinyl)-9-(4-chlorobenoyloxy)-10,11-dihydroquinidine;
acrylonitrile co-polymer of 11-[2-acryloyloxy)ethylsulfonyl]-9-(N,N-dimethylcarbamoyl)-10,11-dihydroquinidine;
acrylonitrile co-polymer of 9-(10-undecanoyl)-10,11-dihydroquinidine.

After stirring for 10 min, the polymer bound olefin (0.125 mmol, 1 eq.) was added in one portion. The reaction mixture was stirred for 24 hrs. To the reaction mixture was added solid sodium metabisulfate (0.400 g), and the mixture was stirred for an additional 5 min. The reaction mixture was filtered, and successively washed with acetone and methylene chloride. The resin was dried over Na_2SO_4 *under vacuo*. i) The resin was suspended in TFA/CH_2Cl_2 (v/v, 95/5) for 30 min. After filtering off the resin, the filtrate was

evaporated to dryness. The % conversion of the olefin to the dihydroxylated product was determined by NMR. A comparision of ^1H olefinic signals of the unreacted cinnamic acid with aliphatic proton signals of the product diol acid allowed assessment of the percent conversion. ii) The resin was suspended in a methanol solution of sodium methoxide. This mixture was stirred for 2 h at room temperature and the solvent was removed *in vacuo*. The mixture was separated by silica gel column chromatography (ethyl acetate/hexane, 1/1). The enantiomeric excess of the product diol was determined through NMR analysis of the derived bis-Mosher ester of this methyl ester.

Method B:

A similar procedure to Method A was followed except acetone/water solvent and methylmorpholine *N*-oxide (NMO) were used. The reaction mixture contained a small aliquot of OsO_4 in *t*-butanol (OsO_4 2.5 wt % solution, 13 µl, 0.01 eq. relative to the olefin), the ligand (0.0025 g, 0.025 eq.), 4-methylmorpholine *N*-oxide (0.022 g, 1.5 eq.), and tetraethylammonium acetate tetrahydrate (0.033 g, 1.0 eq.) in acetone-water (10/1, v/v, 4 ml) at 4 °C.

Synthesis of compound 18 as illustrated in Figure 7. A mixture of dihydroquinidine **15** (5.00 g, 15.32 mmol, 1 eq; Aldrich), 1,4-dichlorophthalazine **16** (3.66 g, 18.38 mol, 1.2 eq; Aldrich), and K_2CO_3 (6.35 g, 45.95 mmol, 3 eq) in dry toluene are refluxed with a concurrent azeotropic removal of water for 2 hr. Then, 85 % KOH pellets (3.02 g, 45.95 mmol, 3 eq) was added at once and the reaction mixture was refluxed until dihydroquinidine disappeared on t.l.c. The light orange solution was cooled to room temeperature, mixed with water, and then extracted with ethyl acetate. The organic layer was dried over sodium sulfate. The removal of solvent and then column chromatogarphy of residue gave the mono-

substituted chlorophthalazine **17** (6.05 g, 81 %), which upon similar transformation with quinidine provided the di-substituted phthalazine **18** (6.76 g, 85 % starting from 5.00 g of **17**). **17**: ^{1}NMR (300 MHz, $CDCl_3$) δ 0.91 (t, J = 6.7 Hz, 3H), 1.40-1.70 (m, 6H), 1.77 (m, 1H), 2.12 (m, 1H), 2.65-3.00 (m, 4H), 3.43-3.58 (m, 1H), 3.99 (s, 3H), 7.27 (d, J = 7.0 Hz, 1H), 7.34 (dd, J = 9.3 & 2.8 Hz, 1H), 7.44 (d, J = 4.5 Hz, 1H), 7.62 (d, J = 2.7 Hz, 1H), 7.96 (d, J = 9.2 Hz, 1H), 8.00 (m, 2H), 8.13-8.20 (m, 1H), 8.33-8.42 (m, 1H), 8.64 (d, J =4.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.9, 23.5, 25.4, 26.1, 27.1, 37.3, 49.9, 50.9, 55.5, 59.9, 101.7, 118.5, 121.4, 121.8, 122.8, 122.9, 125.3, 127.7, 128.2, 131.6, 133.0, 133.3, 144.0, 144.7, 147.0, 147.2, 150.5, 157.7; HRMS (FAB$^+$) calcd for [$C_{28}H_{29}ClN_4O_2$ + H$^+$] = 489.2057, found = 489.2051. **18**: ^{1}NMR (300 MHz, $CDCl_3$) δ 0.78 (t, J = 6.7 Hz, 3H), 1.20-1.65 (m, 10H), 1.68 (m, 1H), 1.85-2.30 (m, 3H), 2.55-3.00 (m, 8H), 3.39 (m, 2H), 3.88 (s, 6H), 4.97 (m, 2H), 5.90 (m, 1H), 6.95 (d, J = 6.5 Hz, 1H), 7.01 (d, J = 5.9 Hz, 1H), 7.34 (m, 2H), 7.40 (d, J = 4.6 Hz, 1H), 7.42 (d, J = 4.6 Hz, 1H), 7.52 (d, J = 2.7 Hz, 1H), 7.54 (d, J = 2.6 Hz, 1H), 7.91 (m, 2H), 7.96 (d, J = 9.2 Hz, 1H), 7.97 (d, J = 9.2 Hz, 1H), 8.31 (m, 2H), 8.61 (d, J = 4.5 Hz, 1H), 8.62 (d, J = 4.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.8, 23.2, 23.4, 25.2, 26.0, 26.2, 26.4, 27.2, 27.7, 37.3, 39.6, 49.4, 49.8, 49.9, 50.8, 55.5, 60.0, 60.2, 76.0, 77.2, 101.9, 102.0, 114.6, 118.2, 118.4, 121.7, 121.8, 122.3, 122.7, 123.0, 127.3, 128.1, 129.0, 131.4, 131.5, 132.0, 132.1, 140.3, 144.6, 144.8, 144.9, 147.3, 156.3, 156.4, 157.5, 157.6; HRMS (FAB$^+$) calcd for [$C_{48}H_{52}N_6O_4$ + H$^+$] = 777.4128, found 777.4104.

Synthesis of Compound 19 as illustrated in Figure 7.

The heating of **18** (6.00 g, 7.73 mmol, 1 eq) and 3-mercaptopropionic acid (3-MPA, 0.821 g, 7.74 mmol, 1 eq) in the presence of 2,2'-azobisisobutyronitrile (AIBN,

0.0635 g, 0.3867 mmol, 0.05 eq) in benzene (70 °C) allowed the isolation of **19** as a tan precipitate (4.43 g, 64 %). This precipitate was already such pure that it was used for the next step without further purification. **19**: ^{1}NMR (300 MHz, $CDCl_3$) δ 0.86 (t, J = 6.7 Hz, 3H), 1.25-3.25 (m, 30H), 3.50 (m, 2H), 3.89 (s, 3H), 3.97 (s, 3H), 6.60 (broad s, 1H), 7.30 (m, 3H), 7.44 (t, J = 4.4 Hz, 2H), 7.49 (broad s, 1H), 7.53 (d, J = 2.3, 1H), 7.63 (d, J = 2.4 Hz, 1H), 7.88 (m, 2H), 7.95 (d, J = 9.2 Hz, 1H), 7.96 (d, J = 9.2 Hz, 1H), 8.19 (d, J = 8.1 Hz, 1H), 8.27 (d, J = 7.7 Hz, 1H), 8.59 (d, J = 4.6 Hz, 1H), 8.64 (d, J = 4.5 Hz, 1H); HRMS (FAB$^+$) calcd for [$C_{51}H_{58}N_6O_6S$ + H^+] = 883.4216, found 883.4242.

Synthesis of Compound 20 as illustrated in Figure 7. A mixture of acid **19** (1.00 g, 1.13 mmol, 1.5 eq), MeO-PEG-NH_2 (3.78 g, 0.756 mmol, 1 eq), N,N-dimethylaminopyridine (DMAP, 0.0231 g, 0.189 mmol, 0.25 eq) and 1,3-dicyclohexylcarbodiimide (DCC, 0.233 g, 1.13 mmol, 1.5 eq) in methylene chloride (DCM) was stirred overnight at room temperature. After the reaction was complete, the insoluble urea side-product was removed by filtration and the pegylated ligand **20** (4.34 g, 98 %) was isolated from the reaction mixture by precipitation following a slow addition of diethyl ether. **20**: ^{1}NMR (300 MHz, $CDCl_3$) δ 0.87 (t, J = 6.7 Hz, 3H), 1.25-2.85 (m, 30H), 3.20-3.75 (PEG peaks), 3.84 (t, J = 6.5 Hz, 2H), 3.88 (s, 6H), 6.59 (broad t, 1H), 6.90 (d, J = 6.6 Hz, 1H), 6.97 (d, J = 5.7Hz, 1H), 7.30 (dd, J = 9.2 & 2.4 Hz, 1H), 7.32 (dd, J = 9.0 & 2.4 Hz, 1H), 7.39 (t, J = 4.6 Hz, 2H), 7.47 (d, J = 2.5 Hz, 1H), 7.51 (d, J = 2.5 Hz, 1H), 7.90 (m, 2H), 7.93 (d, J = 9.0 Hz, 1H), 7.94 (d, J = 9.2 Hz, 1H), 8.28 (m, 2H), 8.59 (d, J = 4.5 Hz, 2H).

Synthesis f Compound 14 as illustrated in Figure 7. To the mixture of the sulfide **20** (4.00 g, 0.682 mmol, 1eq),

and *N*-methylmorpholine-*N*-oxide (NMO, 0.24 g, 2.046 mmol, 3 eq) in acetone/water (v/v, 2/1) was added OsO_4 (1 mol %, 0.01 eq). The resulting reaction mixture was stirred overnight at room temperature, and then quenched with sodium bisulfide (100 mg). The reaction mixture was dried over sodium sulfate, and solid was filtered off. Slow addition of ether to the filtrate separated **14** as a white precipitate (3.90 g, 97 %). **14**: ^{1}NMR (300 MHz, $CDCl_3$) δ 0.79 (3H), 1.10-3.00 (30H), 3.10-3.80 (PEG peaks), 3.80-4.00 (8H), 6.70 (1H), 6.95 (1H), 7.05 (1H), 7.20-7.45 (7H), 7.50 (1H), 7.80-8.10 (4H), 8.28 (1H), 8.37 (1H), 8.55 (2H). Peak mutiplicity was not further characterized due to line-broadening.

General procedure for the attachment of PEG soluble support to the ligand:

A mixture of ligand acid (1.00 g, 1.13 mmol, 1.5 eq., MeO-PEG-NH_2 (3.78 g, 0.756 mmol, 1 eq; Aldrich/ Sigma/ Fluka, etc.), N,N- dimethylaminopyridine (DMAP, 0.0231 g, 0.189 mmol, 0.25 eq) and 1,3-dicyclohexylcarbodiimide (DCC, 0.233 g, 1.13 mmol, 1.5 eq) in methylene chloride (DCM) was stirred overnight at room temperature. After the reaction was complete, the insoluble urea side-product was removed by filtration and the pegylated ligand (4.34 g, 98 %) was isolated from the reaction mixture by precipitation following a slow addition of diethyl ether. Ligand acid can be obtained as described in the following U.S. Patents:

1. from U.S. Patent No. 5,260,461, incorporated herein by reference, ligand acids may be obtained for the following alkaloids:

   1,4-bis-(9'-O-dihydroquinidyl)-phthalazine;
   1,4-bis-(9'-O-quinidyl)-phthalazine;
   3,6-bis-(9'-O-dihydroquinidyl)-pyridazine;
   3,6-bis-(9'-O-quinidyl)-pyridazine; 1,4-bis-(9'-O-dihydroquinyl)-phthalazine;
   1,4-bis-(9'-O-quinyl)-phthalazine;

3,6-bis-(9'-O-dihydroquinyl)-pyridazine; and
3,6-bis-(9'-O-quinyl)-pyridazine;

2. from U.S. Patent No. 4,871,855, incorporated herein by reference, ligand acids may be obtained for the following alkaloids:
dimethylcarbamoyl dihydroquinidine;
benzoyl dihydroquinidine;
4-methoxybenzoyl dihydroquinidine;
4-chlorobenzoyl dihydroquinidine;
2-chlorobenzoyl dihydroquinidine;
4-nitrobenzoyl dihydroquinidine;
3-chlorobenzoyl dihydroquinidine;
2-methoxybenzoyl dihydroquinidine;
3-methoxybenzoyl dihydroquinidine;
2-naphthoyl-dihydroquinidine;
cyclohexanoyl dihydroquinidine;
p-phenylbenzoyl dihydroquinidine;
dimethylcarbamoyl dihydroquinidine;
benzoyl dihydroquinine;
4-methoxybenzoyl dihydroquinine;
4-chlorobenzoyl dihydroquinine;
2-chlorobenzoyl dihydroquinine;
4-nitrobenzoyl dihydroquinine;
3-chlorobenzoyl dihydroquinine;
2-methoxybenzoyl dihydroquinine;
3-methoxybenzoyl dihydroquinine;
2-naphthoyl dihydroquinine;
cyclohexanoyl dihydroquinine; and
p-phenylbenzoyl dihydroiquinone;

3. From U.S. Patent No. 5,126,494, incorporated herein by reference, ligand acids may be obtained for the following alkaloids:
acrylonitrile co-polymer of 9-(4-chlorobenoyloxy)-quinidine;
acrylonitrile co-polymer of 11-((2-acryloyloxy)ethyl-sulfinyl)-9-(4-chlorobenoyloxy)-10,11-dihydroquinidine;

acrylonitrile co-polymer of 11-[2-acryloyloxy)ethylsulfonyl]-9-(N,N-dimethylcarbamoyl)-10,11-dihydroquinidine; and acrylonitrile co-polymer of 9-(10-undecanoyl)-10,11-dihydroquinidine.

General procedure for asymmetric dihydroxylation using ligands attached to PEG support:

Method A:

A small aliquot of OsO_4 in *t*-butanol (OsO_4 2.5 wt % solution, 0.01-0.1 eq) was added to a mixture of $K_3Fe(CN)_6$ (0.250 g, 6 eq. relative to the olefin), K_2CO_3 (0.052 g, 3 eq.), methanesulfonamide (0.012 g, 1 eq.), and the PEG-bound alkaloid ligand **14** (0.025-0.25 eq.) or any of the PEG-bound alkaloid ligands described above, in *t*-butanol-water (1/1, v/v, 4 ml) at room temperature. After stirring for 10 min, the olefin substrate (0.125 mmol, 1 eq.was added in one portion. Permissible substrates include all classes of primary, secondary, tertiary and quaternary substituted olefins described in the prior art for the AD reaction. The reaction mixture was stirred for 24 hours. The reaction mixture was stirred at 4°C or room temperature until the olefin disappeared as judged by TLC. Next, solid sodium metabisulfate (0.500 g) was added, and the mixture was stirred for an additional 5 min, then diluted with methylene chloride (10 ml) and dried over Na_2SO_4. All solids were removed by filtration and washed three times with methylene chloride (3 x 5 ml). The combined filtrates were evaporated to half volume and diethyl ether was slowly added to the mixture under vigorous stirring conditions. The precipitate obtained was collected on a glass filter, washed with absolute ethanol/ethyl ether, and dried *in vacuo* (0.294 g, 98 % recovery of ligand resulted from this procedure). Reduction *in vacuo* of the filtrate gave nearly pure dihydroxylated product. The enantiomeric excess of the diol was determined either by HPLC of the *bis*-acetate of hydrobenzoin on a Pirkle 1A ionic *D*-phenylglycine column or through NMR analysis of the derived bis-Mosher ester.

Method B:

A small aliquot (catalytic amount) of OsO_4 in *t*-

butanol (0.01-0.1 eq) was added to a mixture of the polymer catalyst (PEG-ligand; see Method A for examples of compounds used) (0.025-0.25 eq), 4-methylmorpholine *N*-oxide (1.5 eq), and tetraethylammonium acetate tetrahydrate (1 eq) in acetone-water (10/1, v/v, 4 ml) at 4 °C. After stirring for 10 min, the olefin (1 eq) was added either in one portion or by a slow addition. The reaction mixture was stirred at 4 °C until the olefin disappeared as judged by TLC. Next, solid sodium metabisulfate (0.500 g) was added, and the mixture was stirred for an additional 5 min, then diluted with methylene chloride (10 ml) and dried over Na_2SO_4. All solids were removed by filtration and washed three times with methylene chloride (3 x 5 ml). The combined filtrates were evaporated to half volume and diethyl ether was slowly added to the mixture under vigorous stirring conditions. The precipitate obtained was collected on a glass filter, washed with absolute ethanol/ethyl ether, and dried *in vacuo* (0.294 g, 98 % recovery of ligand resulted from this procedure). Reduction *in vacuo* of the filtrate gave nearly pure dihydroxylated product. The enantiomeric excess of the diol was determined either by HPLC of the *bis*-acetate of hydrobenzoin on a Pirkle 1A ionic *D*-phenylglycine column or through NMR analysis of the derived bis-Mosher ester.

What is claimed is:

1. An improved process for catalyzing a hydroxylation reaction, the process being of a type which includes a step for admixing, within a reaction medium, an olefin, an agent, a catalyst for catalyzing the hydroxylation reaction, and an alkaloid ligand for accelerating the catalysis of the hydroxylation reaction, wherein the improvement comprises:

in said admixing step, the ligand is a PEG bound alkaloid ligand, the PEG bound alkaloid ligand being soluble in the reaction medium and precipitable in a precipitation medium.

2. An improved process for catalyzing a hydroxylation reaction as described in claim 1 wherein the hydroxylation reaction is an asymmetric dihydroxylation reaction and the PEG bound alkaloid ligand is chiral.

3. In a process for catalyzing an hydroxylation reaction,

Step A: admixing an olefin, an agent, a catalyst for catalyzing the hydroxylation reaction, and an alkaloid ligand for accelerating the catalysis of the hydroxylation reaction, said admixing occurring in a reaction medium under reaction conditions for producing an hydroxylation product; then

Step B: admixing a precipitation medium with the reaction medium of said Step A for precipitating the PEG bound alkaloid ligand; and then

Step C: separating the precipitated PEG bound alkaloid ligand of said Step B from the hydroxylation product for recovering the PEG bound alkaloid ligand.

4. In a process for catalyzing an hydroxylation reaction as described in claim 3,

in said step A, the hydroxylation reaction is an asymmetric dihydroxylation reaction and

in said steps A, B, and C, the PEG bound alkaloid ligand is chiral.

5. In a process for catalyzing an hydroxylation reaction,

Step A: admixing one or more reactants with a catalyst for catalyzing the hydroxylation reaction and with a PEG bound alkaloid ligand for accelerating the catalysis of the hydroxylation reaction, said admixing occurring in a reaction medium under reaction conditions for producing an hydroxylation product; then

Step B: admixing a precipitation medium with the reaction medium of said Step A for precipitating the PEG bound alkaloid ligand; and then

Step C: separating the hydroxylation product of said Step B from the precipitated PEG bound alkaloid ligand for obtaing purified product.

6. In a process for catalyzing an hydroxylation reaction as described in claim 5,

in said step A, the hydroxylation reaction is an asymmetric dihydroxylation reaction and

in said steps A, B, and C, the PEG bound alkaloid ligand is chiral.

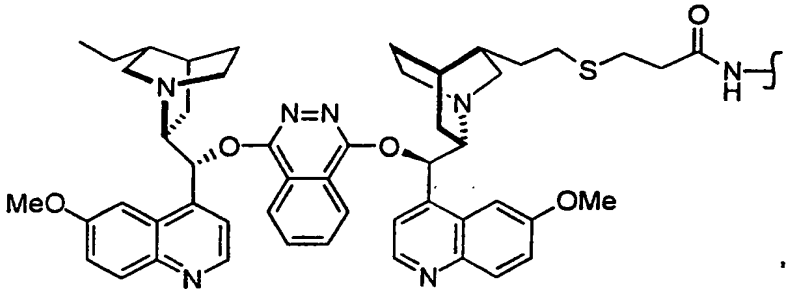
7. A PEG bound alkaloid ligand comprising:

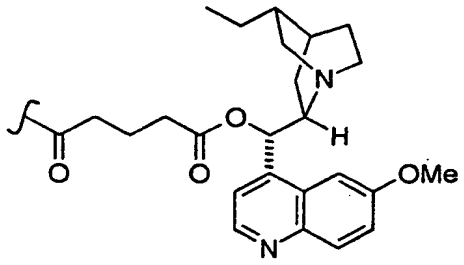
a polyethylene glycol which is soluble in aqueous medium and precipitable in aqueous/ether medium, and

an alkaloid ligand coupled to said polyethylene

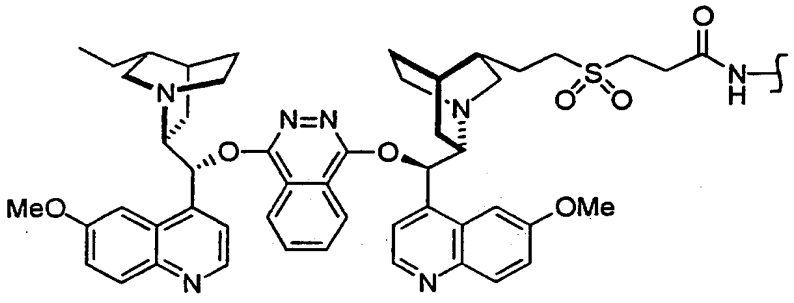
glycol, said alkaloid ligand selected from a group consisting of 1,4-bis-(9'-O-dihydroquinidyl)-phthalazine; 1,4-bis-(9'-O-quinidyl)-phthalazine; 3,6-bis-(9'-O-dihydroquinidyl)-pyridazine; 3,6-bis-(9'-O-quinidyl)-pyridazine; 1,4-bis-(9'-O-dihydroquinyl)-phthalazine; 1,4-bis-(9'-O-quinyl)-phthalazine; 3,6-bis-(9'-O-dihydroquinyl)-pyridazine; 3,6-bis-(9'-O-quinyl)-pyridazine; dimethylcarbamoyl dihydroquinidine; benzoyl dihydroquinidine; 4-methoxybenzoyl dihydroquinidine; 4-chlorobenzoyl dihydroquinidine; 2-chlorobenzoyl dihydroquinidine; 4-nitrobenzoyl dihydroquinidine; 3-chlorobenzoyl dihydroquinidine; 2-methoxybenzoyl dihydroquinidine; 3-methoxybenzoyl dihydroquinidine; 2-naphthoyl - dihydroquinidine; cyclohexanoyl dihydroquinidine; *p*-phenylbenzoyl dihydroquinidine; dimethylcarbamoyl dihydroquinidine; benzoyl dihydroquinine; 4-methoxybenzoyl dihydroquinine; 4-chlorobenzoyl dihydroquinine; 2-chlorobenzoyl dihydroquinine; 4-nitrobenzoyl dihydroquinine; 3-chlorobenzoyl dihydroquinine; 2-methoxybenzoyl dihydroquinine; 3-methoxybenzoyl dihydroquinine; 2-naphthoyl dihydroquinine; cyclohexanoyl dihydroquinine; *p*-phenylbenzoyl dihydroiquinone; acrylonitrile co-polymer of 9-(4-chlorobenoyloxy)-quinidine; acrylonitrile co-polymer of 11-((2-acryloyloxy)ethyl-sulfinyl)-9-(4-chlorobenoyloxy)-10,11-dihydroquinidine; acrylonitrile co-polymer of 11-[2-acryloyloxy)ethylsulfonyl]-9-(N,N-dimethylcarbamoyl)-10,11-dihydroquinidine;

acrylonitrile co-polymer of 9-(10-undecanoyl)-10,11-dihydroquinidine; and alkaloid ligand represented by the following structures:



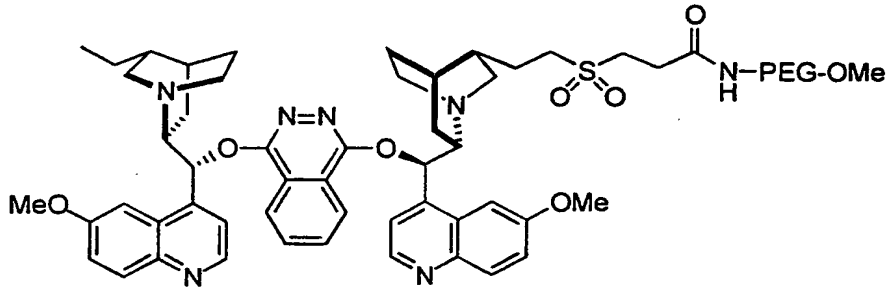


and

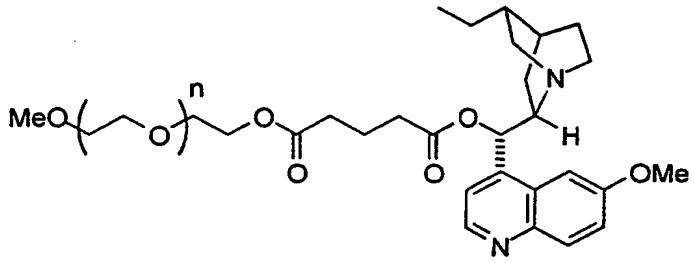


8. A PEG bound alkaloid ligand as described in claim 7 wherein said alkaloid ligand is coupled to said polyethylene glycol by a linkage selected from the group consisting of ester linkage, amide linkage, thoester linkage, ester linkage, thiether linkage, and sulphone linkage.

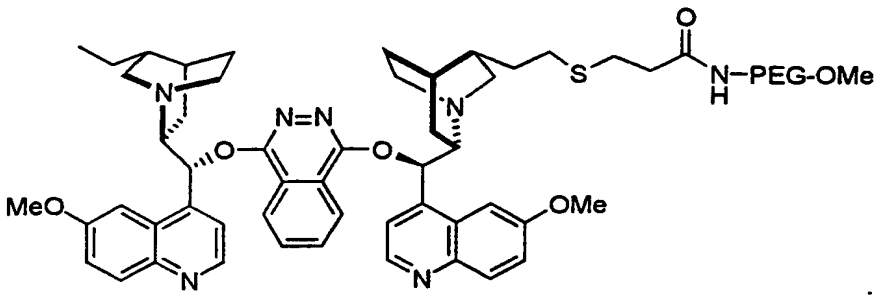
9. A PEG bound alkaloid ligand as described in claim 7 represented by the following structure:

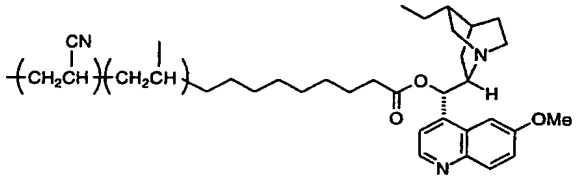


10. A PEG bound alkaloid ligand as described in claim 7 represented by the following structure:

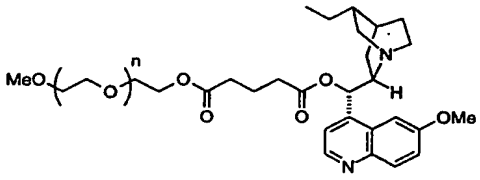


11. A PEG bound alkaloid ligand as described in claim 7 represented by the following structure:

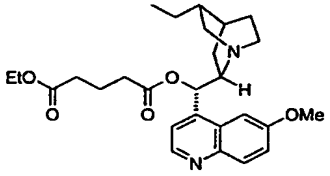




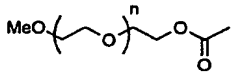
1



2

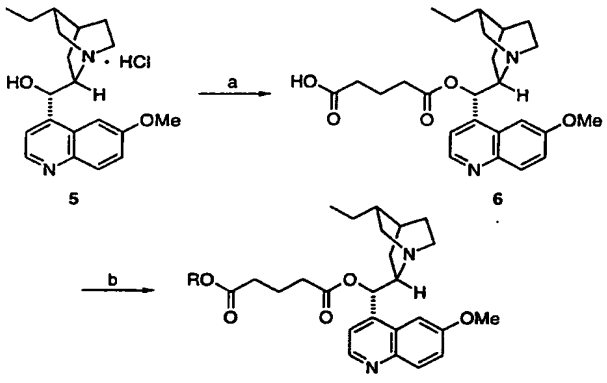


3



4

FIGURE 1



2; R = Polyethylene glycol
3; R = Ethyl

FIGURE 2

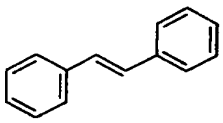
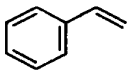
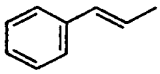
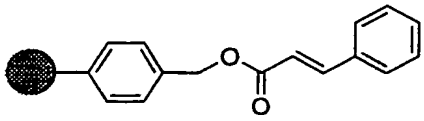
Entry	Catalyst	Olefin	Reaction Time	Yield (%)	ee (%)
1	1		48 h	87	82[b]
2	2		4 h	89	88
3	2[c]		4 h	89	87
4	2[c]		4 h	89	88
5	2[c]		4 h	89	88
6	2[c]		4 h	89	87
7	2[c]		4 h	89	87
8	3		4 h	89	88
9	4		4 h[d]	5	0
10	2		5 h[e]	80	60
11	3		5 h[e]	80	60
12	2		5 h[e]	80	84
13	3		5 h[e]	80	85

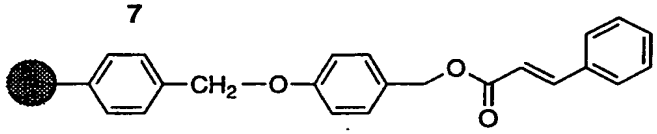
FIGURE 3

Merrifield Resin:



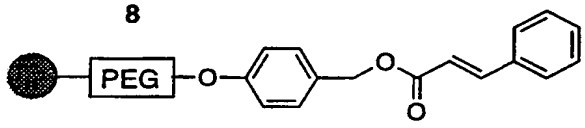
7

Wang Resin:



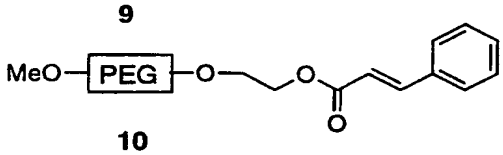
8

Tentagel Resin:

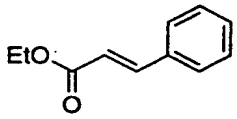


9

PEG:

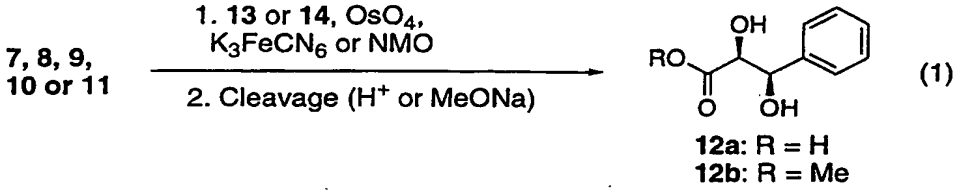


10



11

FIGURE 4


7, 8, 9,
10 or 11
1. 13 or 14, OsO4,
K3FeCN6 or NMO
2. Cleavage (H+ or MeONa)
OH
RO
O
OH
12a: R = H
12b: R = Me
(1)

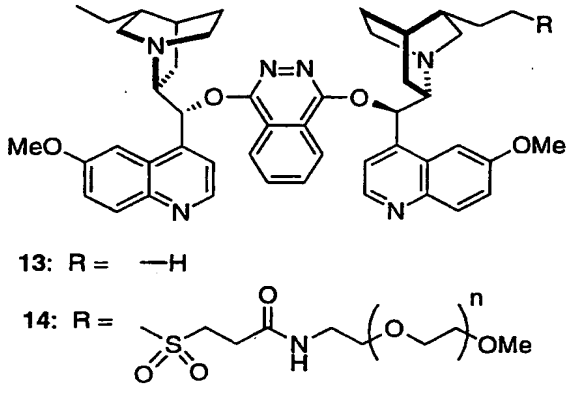

N
N=N
O
O
R
MeO
OMe
N
N
13: R = —H
14: R =
O
S
O
O
N
H
n
O
OMe

FIGURE 5

Entry	Polymer-olefin	Reaction time (hr)	OsO_4 [a]	Method [b]	% conversion [c]	*ee* [d]
1	**7**	72	0.01	A	-	-
2	**8**	72	0.01	A	-	-
3	**9**	24	0.01	A	3	99
4	**9**	24	0.02	A	63	98
5	**9**	24	0.10	A	96	99
6	**10**	0.5	0.10	A	100	99
7	**7**	24	0.01	B	100	88
8	**8**	24	0.01	B	100	90
9	**9**	24	0.01	B	100	87
10	**10**	24	0.008	A	80	97
11	**11**	24	0.008	A	100	97
12	**9**	24	0.02	A	60	98

FIGURE 6

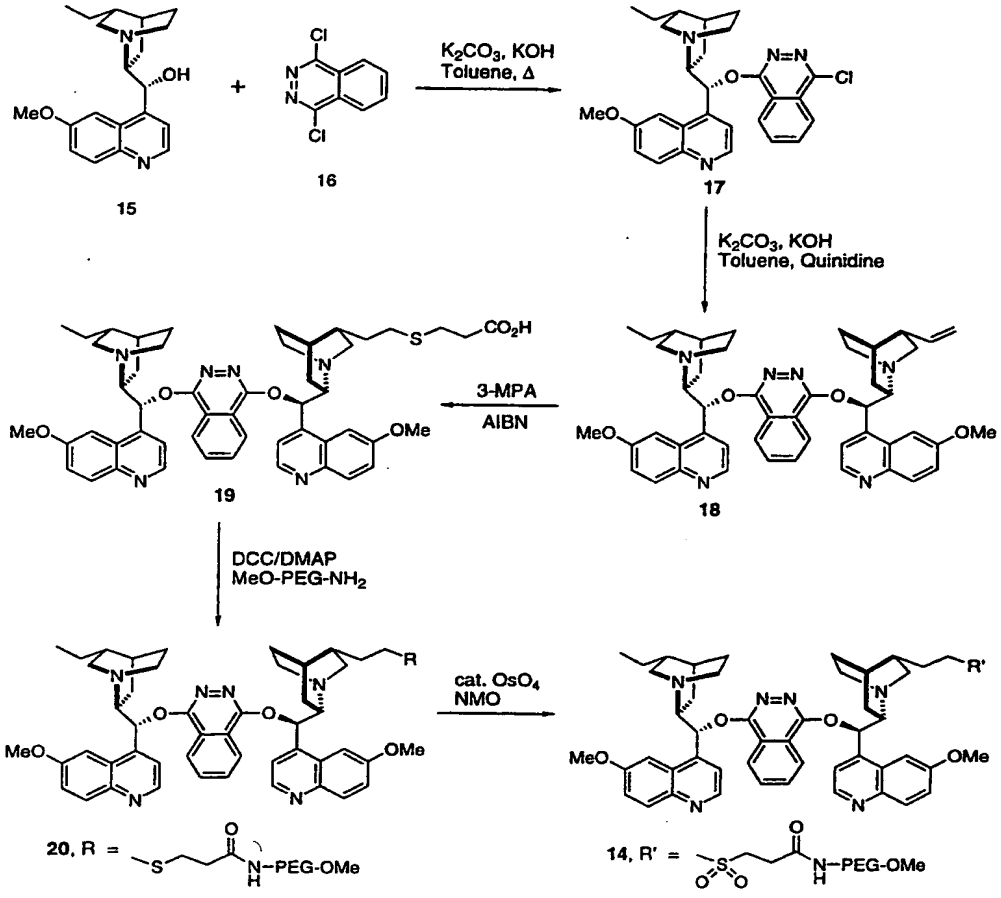

15
16
17
18
19
20, R =
14, R' =
K_2CO_3, KOH
Toluene, Δ
K_2CO_3, KOH
Toluene, Quinidine
3-MPA
AIBN
DCC/DMAP
MeO-PEG-NH_2
cat. OsO_4
NMO
MeO
OMe
N=N
Cl
CO_2H
S
N
O
H
PEG-OMe

FIGURE 7

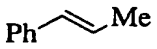
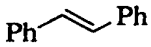
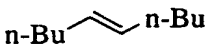
Entry	Olefin	Oxidant	Yield (%)	*ee* (%)
1		NMO	87	72
2		K_3FeCN_6	88	98 (97)[b]
3		NMO	87	91
4		K_3FeCN_6	83	99 (99)[b]
5		NMO	98	94
6		K_3FeCN_6	95	99 (>99)[b]
7		NMO	84	80
8		K_3FeCN_6	80	97 (97)[b]

FIGURE 8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/02442

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07C 29/03 ; C07D 401/14 ; C07D 453/04

US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 568/896 ; 544/233, 238, 240 ; 546/134

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 92/20677 A1 (MASSACHUSETTS INSTITUTE OF TECHNOLOGY) 26 November 1992, entire document.	1-11
A	COREY et al. ' Kinetic Investigations Provide Additional Evidence That an Enzyme-like Binding Pocket Is Crucial for High Enantioselectivity in the Bis-Cinchona Alkoid Catalyzed Assymetric Dihydroxylation of Olefins'. J. Am. Chem. Soc. January 1996, Vol 118, No. 2, pages 319-329, entire document.	1-11

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 05 APRIL 1997	Date of mailing of the international search report 23 APR 1997
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer JEAN F. VOLLANO Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/02442

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ZHANG et al. 'Nonlinear effects involving two competing psuedo-enantiomeric catalysts: example in asymmetric dihydroxylation of olefins'. Tetrahedron: Asymmetry. November 1995, Vol. 6, No. 11, pages 2637-2640, entire document.	7-11
A	SONG et al. 'Polymeric cinchona alkaloids for the heterogeneous catalytic asymmetric dihydroxylation of olefins: the influence of the polymer backbone polarity on the compatibility between polymer support and reaction medium' November 1995, Vol. 6, No.11, pages 2687-2694, entire document.	1-11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/02442

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

568/896 ; 544/233 ; 546/134

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

APS, CAS ONLINE
search terms: hydroxylation reaction, alkaloid ligand, chiral, asymmetric, olefins, alkenes, peg, carbowax, ligand, cinchona, dihydroquinidine